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REMARKS

Entry of the foregoing amendments to the application is requested on the grounds that the claims, as amended, patentably distinguish over the cited art of record or, alternatively, place the application in better condition for appeal. The claims more particularly point out and distinctly claim the subject matter which Applicant regards as the invention. No new issues have been added which would require further consideration and/or search, nor has any new matter been added. The claims as amended are believed to avoid the rejections applied in the Final Office Action for reasons set forth more fully below.

The Office Action of May 28, 2003 has been received and carefully reviewed. It is submitted that, by this Communication, all bases of rejection and objection are traversed and overcome. Upon entry of this Amendment, Claims 1-20, 22, 23, 25-30, 32-38 and 40-55 remain in the application. Reconsideration of the claims as amended is requested.

Claims 1-20, 22-23, 25-30, 32-38 and 40-55 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner states that in claims 1, 11, 23, 34 and 52, it is unclear whether the "medium into which the hydrogel system is introduced" is different from the "medium or mixture into which the three-dimensional hydrogel cross-linking was performed."

Applicant fails to see the language "medium or mixture into which the three-dimensional hydrogel cross-linking was performed" in any of claims 1, 11, 23, 34 or 52. In each of these claims, the medium is first introduced by the article "a," and appears after the hydrogel/hydrogel system is formed. As such, it is submitted that there is no lack of clarity between the mixture to which is added a calcium releasing compound to form the hydrogel/hydrogel system, and the medium into which the thus formed hydrogel/hydrogel system is introduced.

However, in order to expedite prosecution, Applicant has recited "separate" between "a" and "medium" to more particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner is respectfully directed to the following areas of the instant specification which show that the medium into which the hydrogel/system is introduced is separate from the mixture which renders the hydrogel/system:

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The crosslinking density [of the solution forming the gel] was adjusted with a multiplication factor to this molar ratio as a relative calcium ion content, such as 0.5X (molar ratio: 0.09), 1.5X (molar ratio: 0.27), 2X (molar ratio: 0.36), and so forth. (Specification, page 9, lines 24-27)

Sets of three circular gel discs prepared from 3.18% LH alginate with 1.5X [molar ratio: 0.27] CaCO_3 were immersed in saline (0.9% NaCl aqueous solution) adjusted to varying calcium ion concentrations (Figure 7). The alginate gels swelled when the calcium ion concentration was low (0.0005 and 0.0010 M) while the gels shrank when the calcium ion concentration was high (0.0040 M). (Specification, page 16, lines 3-8)

As such, it is submitted that the 112, second paragraph rejection has been traversed and overcome, withdrawal of which is respectfully requested.

Claims 1-20, 22-23, 25-38 and 40-55 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Draget et al (1991) in view of Martinsen et al. (1989), further in view of Hauselmann et al (US Patent 5,658,343) and Cao et al (1996).

As to Draget, Hauselmann and Cao, the Examiner repeated his rejections from previous Office Actions. As to Martinsen, the Examiner states that this reference teaches evaluation of stability of Ca-alginate gel beads towards Na^+ ions by transferring gel beads to solutions containing different concentrations of CaCl_2 and measuring the bead volume (shrinkage) every 24 hours for 3 days. The Examiner further states that Martinsen teaches that gel strength and shrinkage is the function of CaCl_2 concentration and gelling time (Page 84, col. 1-2, Figs. 7 and 8). In addition, the Examiner states that Martinsen teaches that high gel strength, low shrinkage, high stability towards Na^+ ions and high permeability of alginates are the most advantageous factors for the immobilization of living cells.

As such, the Examiner concludes that it would have been obvious in view of Martinsen to control the hydrogel shrinkage or swelling by transferring the hydrogels into solutions that contain different concentration of calcium ions.

In sharp contrast to the Examiner's assertions, Applicant submits that none of the cited references teach or suggest **selective** size control of a three dimensional hydrogel system by varying cation concentration of a separate medium into which it is introduced.

Draget is silent as to transferring a hydrogel into a medium. As such, the Examiner's assertion that Draget teaches that variation in calcium ion concentration results in the *formation*

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of hydrogels with distinct characteristics is off point. Applicant's invention as defined in claims 1, 11, 23, 34 and 52 recites that shrinking, swelling or maintaining of the (*already formed*) hydrogel is selectively controlled by varying a calcium ion concentration of a separate medium into which the hydrogel is introduced.

The '343 patent controls the hydrogel system by a mechanical means (the boundary layers). The passage referred to by the Examiner (Col. 7, lines 29 et seq.) speaks of molar ratio of calcium ions to carboxyl groups in the gel to determine the amount of crosslinking--in sharp contrast, Applicant's invention as defined in claims 1, 11, 23, 34 and 52 recites selective control of the hydrogel system by varying cation/calcium ion concentration in a separate medium into which the hydrogel is introduced.

Martinsen, which was cited by Applicant in the present application, is an example of a traditional means of creating alginate gel beads. 1) Beads are the only structure which can be formed by Martinsen's method; this is in sharp contrast to Applicant's inventive hydrogel as defined in the pending claims, which may take any three dimensional shape. 2) The Martinsen beads are formed by allowing droplets of sodium alginate solution to fall into an aqueous solution of CaCl_2 ; this is in sharp contrast to Applicant's method as defined in relevant pending claims, Applicant's hydrogel is **not** formed in a calcium solution. 3) The crosslinking density of the Martinsen-formed beads is NOT uniform--the surface is highly crosslinked, and the interior has a low (if any) crosslinking density (this is known in the art); this is also in sharp contrast to Applicant's inventive hydrogel as defined in the pending claims, which is uniformly crosslinked and is structurally homogeneous. Since Applicant's hydrogels are not formed in calcium solutions, the inventive hydrogels do not have a layer (shell) of surface crosslinking, and are therefore open pored, thus calcium ions can move in and out of the hydrogel.

In Figs. 9 and 10 of Martinsen, the authors were studying how calcium competes with sodium, and how stable the gel beads were. (Figs. 7 and 8 of Martinsen are irrelevant to Applicant's recitation of selectively controlling shrinking, swelling or maintaining of the hydrogel system by varying a calcium ion concentration of a medium into which the hydrogel system is introduced--Figs. 7 and 8 speak to the calcium chloride concentration of the solution used for gelation.) This is very different from Applicant's selective control of the size of the hydrogel/hydrogel system. Martinsen at p. 89, Col. 1, states that "[a]s a result, when calcium

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ions are present in sufficient amounts to counterbalance the osmotic pressure in the gel (Fig. 8), and to saturate the binding sites despite the competition from sodium ions (Fig. 10), and after binding has proceeded to a maximum on the time scale (Fig. 12), further physical changes are small in the gel system. (emphasis added)

As can be seen, Martinsen is NOT describing selective control of the size of a hydrogel—as quoted above, once all the binding sites (at the surface) are full, “further physical changes are small.” However, in sharp contrast, Applicant can selectively cause the inventive hydrogel to swell, shrink or maintain by varying a calcium ion concentration of a separate medium into which the hydrogel system is introduced.

In summary regarding Martinsen: a) the composition and structure of the Martinsen hydrogel beads is quite different from the three dimensional, uniformly crosslinked and structurally homogeneous hydrogel system of Applicant's invention as defined in the claims; b) Martinsen's aim in Figs. 9 and 10 was to study competition between sodium and calcium ions; and c) Martinsen admits that after surface binding sites are full, physical changes are small.

Due to the disparity between Martinsen's hydrogel beads and Applicant's hydrogel, the skilled artisan would not have been taught and/or led to believe by Martinsen that if he placed Applicant's structurally homogeneous, three dimensional hydrogel (NOT formed in a calcium solution) in Martinsen's 0.9% NaCl solution, that he would be able to selectively control the shrinking, swelling or maintaining of Applicant's hydrogel by varying the concentration of the CaCl_2 . In fact, Martinsen was published in 1989, and researchers in tissue engineering have been searching for a means of controlling the size of a formed hydrogel; however, prior to Applicant's invention as defined in the pending claims, the efforts had been unsuccessful. This would lead one to believe that Martinsen did NOT teach what the Examiner is asserting the publication taught.

It is further submitted that the Examiner is using hindsight to assume that Martinsen was teaching volume control of a non-bead, uniformly crosslinked hydrogel. The Examiner assumes that **different** hydrogel structures, formed by **different** methods will react the **same** in calcium ion solutions. Yet, the Examiner cites no evidence to buttress this theory. This assertion by the Examiner flies in the face of the oft-cited maxim that chemistry is an “unpredictable” art.

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As such, it is submitted that Applicant has rebutted the Examiner's case of prima facie obviousness.

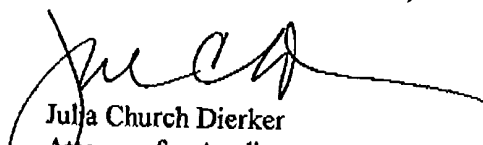
For all the above reasons, it is submitted that Applicant's invention as defined in independent claims 1, 11, 23, 34 and 52, as well as in all claims dependent therefrom, is not anticipated, taught or rendered obvious by Draget, Martinsen, Cao or '343, either alone or in combination, and patentably defines over the art of record.

In summary, Claims 1-20, 22, 23, 25-30, 32-38 and 40-55 remain in the application. Claims 1, 11, 23, 32, 34, 52 and 55 have been amended. It is submitted that, through this amendment, Applicant's invention as set forth in these claims is now in a condition suitable for allowance. Should the Examiner believe otherwise, it is submitted that the claims as amended qualify for entry as placing the application in better form for appeal.

Further and favorable consideration is requested.

Respectfully submitted,

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